

Spring 5-2015

Bio-Identical Hormones Utilized for Treating Menopausal Symptoms: Are They Safe?

Maria D. White

Northern California Consortium, Doctor of Nursing Practice Program, California State University, Fresno and San José State University

Follow this and additional works at: https://scholarworks.sjsu.edu/etd_doctoral

Part of the [Other Nursing Commons](#)

Recommended Citation

White, Maria D., "Bio-Identical Hormones Utilized for Treating Menopausal Symptoms: Are They Safe?" (2015). *Doctoral Projects*. 22.
DOI: <https://doi.org/10.31979/etd.e2ht-8zmu>
https://scholarworks.sjsu.edu/etd_doctoral/22

This Doctoral Project is brought to you for free and open access by the Master's Theses and Graduate Research at SJSU ScholarWorks. It has been accepted for inclusion in Doctoral Projects by an authorized administrator of SJSU ScholarWorks. For more information, please contact scholarworks@sjsu.edu.

BIO-IDENTICAL HORMONES
UTILIZED FOR TREATING
MENOPAUSAL SYMPTOMS: ARE THEY SAFE?

By
Maria D. White

A doctoral project in partial fulfillment of the
requirements for the degree of Doctorate of Nursing
Practice in the California State University, Northern
Consortium, Doctor of Nursing Practice Program,
California State University, Fresno

May 2015

APPROVED

For the Department of: Nursing

We, the undersigned, certify that the thesis of the following student meets the required standards of scholarship, format, and style of the university and the student's graduate degree program for the awarding of the doctorate's degree.

Maria D. White
Thesis Author

Christine Ortiz

Chairperson Christine Ortiz (Chair)

Nursing

Moses Laufer

Committee member Moses Laufer

Holtorf Medical Group

Victoria Orton

Committee member Victoria Orton

El Camino College

For the University Graduate Committee:

Dean, Division of Graduate Studies

AUTHORIZATION FOR REPRODUCTION OF DOCTOR OF NURSING
PRACTICE PROJECT

I, *Maria D. White*, grant permission for the reproduction of this project
(*Bio-identical Hormones Utilized for Treating Menopausal Symptoms: Are They Safe?*)
in part or in its entirety without further authorization from me, on
the condition that the person or agency requesting reproduction
absorbs the cost and provides proper acknowledgment of
authorship.

Signature of DNP Project Author *Maria D. White*

Date *May 15, 2015*

Dedication

This doctoral project is dedicated to my parents Art Duarte and Cora Duarte who both encouraged me to obtain my education no matter what obstacles were in my path. Each of you believed that I could do anything, even when I was unsure of myself thank you and I love you both.

Acknowledgments

First I would like to thank my family, my husband Dave, my daughter Kandis, Angelo, my grandchildren Hailey, Andruw, and Kendal. My sisters' Polly and Sharon for their love and support you each gave me encouragement, strength, and love throughout my doctoral program. Everyone has given me understanding and patience when I needed it most, I could have never done this without each of you.

I would like to thank my doctoral advisor and chair Christine Ortiz for her direction, support, encouragement, and mentorship during the program. Committee members Moses Laufer, your commitment to bioidentical hormone therapy was appreciated and Victoria Orton whose commitment to helping me achieve my goal by offering guidance and support when I needed it most, I am forever grateful. Dr. Kent Holtorf thank you for granting me your consent to proceed with this project and Adam Smith my statistician, thank you for working the numbers for this project. Lastly thank you to a few of my amazing DNP cohort colleagues, for giving me encouragement and being on this journey with me I know we will continue to stay close

Finally I would like to thank the women who have sought an alternative form of hormonal treatment that provided me with the necessary information for this project.

Bio-identical Hormones
Utilized For Treating
Menopausal Symptoms: Are They Safe?

By

Maria D. White, DNP, RN, MSN-ACNP

California State University, Northern California Consortium

Doctor of Nursing Practice

School of Nursing

May 14, 2015

Table of Contents

Abstract.....	4
Introduction.....	5
Chapter 1.....	5
Theoretical Framework.....	6
Background.....	8
Chapter 2.....	9
Review of the Literature.....	9
Effects of Menopause.....	13
Results of Estrogen Loss.....	17
Chapter 3.....	29
Methods.....	29
Project Design.....	29
Setting.....	30
Sample.....	30
Instrumentation.....	31
Data Collection.....	31
Data Collection Procedures.....	32
Data Analysis	32
Ethical Consideration (Human Subject Protections).....	32
Chapter 4.....	32
Results.....	32
Demographics.....	34

Descriptive statistics.....	37
Inferential statistics.....	39
Chapter 5.....	45
Discussion of the Results.....	45
Summary.....	48
Limitations.....	49
Bias.....	50
Implications for Nursing Practice and Conclusion.....	50
References.....	51
Appendix A Tool.....	64
Appendix B Holtorf Approval Letter.....	66
Appendix C Fresno State Institutional Review Board Letter.....	67

Abstract

The use of compounded bioidentical hormones in the various forms of gels, creams, and troches has increased in popularity. The population of menopausal women is at a crossroads with the cascade of symptoms and determining what are their options. The Endocrine Society, the Food and Drug Administration, and the National Menopause Society do not support the use of bioidentical hormones, despite the support for bioidentical hormone replacement therapy (BHRT) by the American Academy for Anti-Aging Medicine and other proponents for BHRT. The literature review reveals the need for studies documenting the safety of BHRT. The objective for this study was to conduct a retrospective chart review for the incidence of adverse outcomes specific to osteoporosis, breast cancer incidence, and cardiovascular disease in menopausal women utilizing BHRT.

Chapter 1

Introduction

The use of bio-identical hormone replacement therapy (BHRT) for the alleviation of menopausal symptoms is being selected by women in the United States (US) (Watt, Hughes, Rettew, & Adams, 2003), however the research regarding BHRT is limited. Pharmaceutical treatment for menopausal symptoms is a topic of debate and has received significant attention by women, the media, the Food and Drug Administration, and the medical field (Garber, 2008; North American Menopause Society (NAMS), 2010; Rosenthal, 2008; Rossouw et al., 2007). Since the publication of the results of the Women's Health Initiative trial (WHI) announcing the increased risk for stroke, venous thrombosis, and breast cancer, and with no favorable outcome on coronary heart disease (CHD), there has been an increase in alternative approaches to the types of hormone replacement therapy (Cirigliano, 2007).

In 2010, nearly 23 million women living in the United States were between the ages of 45 and 54 (U.S. Census Bureau, 2010), while the average age for natural menopause in the United States is 51 (NAMS, 2013). The midlife symbolizes many lifestyle and biological changes for women that include the transition to menopause. It is estimated women may live approximately 30 years following menopause (Warren & Valente, 2004). This increase in longevity from earlier decades thereby places the risk for age-related health conditions that affect post-menopausal women. The incidence of most chronic conditions such as colon cancer, cardiovascular disease, Alzheimer's disease and osteoporosis increases in the post-menopausal phase of a woman's life (Shoupe, 2012).

The period of time prior to menopause is referred to as perimenopause, and during this stage, symptoms occur from the decrease in ovarian function and estrogen production eventually

ceases (Holloway, 2011), also referred to the menopausal transition time (Bastian, Smith, & Nanda, 2003; Meleis, Sawyer, Im, Messias, & Schumacher, 2000). This period of transition is often signified as a phase of unpredictable hormone fluctuations preceding menopause (Nelson, 2008) and the onset of fluctuations in reproductive hormones preceding natural menopause in women (Bastian, Smith, & Nanda, 2003). Smoking and low-socioeconomic status are associated with premature final menstrual periods, as well as age at menarche, parity, previous oral contraceptive use, body-mass index, ethnic origin, and family history (Nelson, 2008).

The purpose of this project was to investigate if the use of Biest and Progesterone after four years or longer increased the risk for:

1. Osteoporosis.
2. Breast cancer.
3. Cardiovascular disease.

Theoretical Framework

The *Transition Theory* by Meleis was used to frame this project, as menopause is a period of time for women when they are transitioning from a stage in their life of being fertile to the next stage of being non-fertile (Im & Meleis, 2000). The major concepts of Meleis' middle range transition theory include: a) types and patterns of transitions; b) properties of transition experiences; c) transition conditions; d) process indicators; e) outcome indicators; and f) nursing therapeutics (Meleis, Alligood, & Tomey, 2006). Properties within Transition theory consist of awareness, engagement, change and difference, time span, and critical points and events (Im & Meleis, 2000; Meleis, 2010), which can be applied to a woman experiencing symptoms during perimenopause and menopause.

The development of the transition theory originated in the mid-1960's, while Meleis was

working on her PhD, beginning the development of her theoretical journey (Im, 2013). The concept of transition is associated with developmental theory and the stress adaptation theory. One of the important attributes of transition is that it is essentially positive. The resolution of transition denotes the individual has achieved greater steadiness comparable with the pre-transition state. Subsequently Meleis' research became focused on individuals unable to formulate healthy transitions and the unhealthy transitions or unsuccessful transitions in relation to role deficiency (Im, 2013).

The sources utilized in the development of the *Transition Theory* included Meleis' education in nursing, sociology, symbolic interactionism, and role theory. Meleis's initial theory included development of role deficiency and role supplementation in the 1970's. Collaboration with Norma Chick from Massey University, New Zealand lead to further development of the transition theory, resulting in the publication of Meleis's initial article on transitions in nursing in 1985 (Im, 2013). Subsequently, Meleis worked with Karen Schumacher, a doctoral student at the University of California, San Francisco; it was during this time when an extensive literature search was conducted and the discovery of massive use of transition was used in the nursing literature (Im, 2013). Their literature review identified 310 articles focused on transition as a concept in the nursing literature; Meleis subsequently further elaborated on the transition framework (Schumacher & Meleis, 1994).

The defining qualities of transition include process, disconnectedness, perception, and patterns of response (Meleis, 2010). The following events lead to a process of transition including: illness, recovery, birthing, death, loss, immigration, migration, hospitalization, pregnancy, retirement, and maturation (Meleis, 2010). Therefore the use of transition theory can be applied to menopause in women and has been utilized in previous menopause studies as

evidence by the seminal study by Im and Meleis (2000). This study included 119 first generation Korean immigrant women, while Marnocha, Bergstrom, and Dempsey (2011) evaluated 13 women for the meanings of menopause in a qualitative study. Hall, Callister, Berry, and Matsumura (2007) described the attitudes and sociocultural influences in women in the management of menopause within the literature utilizing Meleis's transition theory.

The transition theory includes the property of awareness is defined as a perception, knowledge, and recognition of a transition experience and level of awareness, as this relates to what is known about the process and responses of the individuals undergoing similar transitions (Meleis et al., 2000). The property of awareness can be associated with a woman experiencing hot flashes or changes specific to her menstrual cycle, from regular to varying in time of onset. The property of engagement is referred to as the degree in which a woman demonstrates involvement in the process inherent in the transition, a level of awareness related to a level of engagement (Meleis et al., 2000). The woman with a level of engagement is aware of physical and emotional changes specific to her body, as they relate to menopausal symptoms. Perimenopause and menopause are also considered periods of time for women that are normal life transitions (Meleis, 2010).

Background

The background for this project focuses on the symptoms of menopause, treatment of menopause and the prescribed pharmaceutical hormone replacement therapy utilized. The prescribed pharmaceutical hormone replacement therapy was addressed and included synthetic preparations known as Premarin, and compounded hormone therapies known as bioidentical hormones (BH). Compounded hormones have increased in utilization because of the initial results from the Women's Health Initiative (WHI) (2002), as a result of celebrity endorsements,

media coverage, and expansion of bioidentical hormone therapy industry (Files, Ko, & Pruthi, 2011).

Chapter 2

Review of the Literature

The literature review is arranged to address BH, the main areas of menopause, traditional hormone replacement therapy, and establish a framework to guide the research investigation. The information presented includes bioidentical hormones, physiology of perimenopause, physiology of menopause, the effects of menopause, osteoporosis, diagnosis of osteoporosis, the landmark studies specific to osteoporosis, the results of estrogen loss and the development of insulin resistance, the landmark studies related to insulin resistance, and the development of cardiovascular disease and the landmark studies, stroke, venous thrombosis, and breast cancer. The use of hormone replacement therapy including study results, the current controversies surrounding BHRT, BHRT studies, and the current recommendations for treating women with menopausal symptoms were addressed.

Bioidentical Hormones

The impact of the WHI (Rossouw et al., 2002), study resulted in women discontinuing hormone replacement therapy (HRT), while moving to an alternative form of treatment, known as compounded bioidentical hormones (CBH) (Cirigliano, 2007). Additionally, the celebrity books by Suzanne Somers *The Sexy Years*, and Michael Platt's *The Miracle of Bioidentical Hormones*, spurred interest for women seeking an alternative form of treatment for menopausal symptoms post WHI results (Cirigliano, 2007). Subsequently, Somers wrote another book *Ageless: The Naked Truth About Bioidentical Hormones*, supporting the use of bioidentical hormones as reversing the aging process, keeping one mentally sharp, physically fit, and sexually

active, with no clinically proven data to support her statements (Cirigiliano, 2007).

The process of compounding is described as the mixing of a drug by a pharmacist with a licensed practitioner's prescription. The pharmaceutical companies accepted most of the compounding in the 1900's, resulting in a decrease of compounding by pharmacists. The United States Food and Drug Administration (USFDA) supports the compounding of prescriptions as being ethical and legal (Pegues, 2006), while it is estimated that 1% of prescriptions in the United States, (approximately 30 million per year) are compounded (Endocrine Society, 2006). The practice of compounding is also popular in Europe (Cirigiliano, 2007).

Bioidentical hormones (BH) are characteristically derived from plant extracts and chemically altered to be identical in structure to endogenous human hormones (Cirigiliano, 2007; Sites, 2008). The sources of these hormones include plants from soy or yam, with a fundamental primary concept being supported that isomolecular hormones are identical to those found in a woman and therefore are better tolerated and more appropriate to treat menopausal symptoms (Lorentzen, 2001; Walker, 2001). Compounded bioidentical estrogens include estrone (E-1) and estradiol (E-2). Prior to January 2008, estriol (E-3) was available (Eichelsdoerfer, 2008). These estrogens (estriol, estradiol and estrone), when combined, are referred to as "biest" (bi-estrogen) with estriol and estradiol and "tri-est" with all three estrogens (Eichelsdoerfer, 2008).

Bioidentical hormones have been traced to Jonathan Wright, as he described the physiologic difference noted between patentable and un-patentable hormones (Wright & Morganthaler, 1997; Wright, 2005). Boothby, Doering, and Kipersztak (2004), defined bioidentical hormone replacement therapy (BHRT) as hormone treatment with individually compounded recipes of certain steroids in various dosage forms, that include dehydro-epiandrosterone (DHEA), pregnenolone, testosterone, progesterone, estrone, estradiol, and estiol;

and the use of the term “natural” refers to steroid hormones occurring naturally in women and not in reference to phytoestrogens (Boothby et al., 2004). Fugh-Berman and Bythrow describe BH as “pseudoscientific” referring to endogenous hormones which are synthesized or semi-synthesized (2007).

The dose, regimen, and dosage forms are then customized to treat a menopausal woman’s symptoms, based on hormonal levels, symptoms, and their preferences, also referred to as personalized medicine (Ruiz, Daniels, Barner, Carson, & Frei, 2011). Bioidentical hormones are mixed by a compounding pharmacist, based on a physician’s orders, and administered via transdermal, vaginal, or sublingual routes (Mahmud, 2010). Advocates of custom BHRT claim they offer improved safety, efficacy, and tolerability because of the formulas being individualized, the source of the hormones and the routes of delivery (Boothby et al., 2004).

Physiology of Perimenopause

Perimenopause is known as the physiologic response to the fluctuation of hormones and associated with menstrual cycle irregularity (Bosarge & Freeman, 2009). Perimenopause signifies “around menopause” and denotes the phase during the time which a woman’s body creates her natural change toward permanent infertility (menopause). Perimenopause is also known as “menopausal transition”, the time leading up to menopause (Nelson, 2008). The physiology of perimenopause is often evident by irregular menses, until 12 months after the final menstrual cycle, when a woman is then considered menopausal (National Institutes of Health State, 2005).

The symptoms frequently associated with the onset of perimenopause include irregular menses, vasomotor changes (night sweating and hot flashes), vaginal dryness, mood swings, disruptive sleep patterns, genitourinary changes, sexual dysfunction, anxiety, noticeable changes

in skin characteristics, decreased concentration and depression (Plonczynski & Plonczynski, 2007). Hot Flashes are among the most commonly reported perimenopausal symptoms worldwide and this incidence is one of the motivating reasons for women seeking therapeutic treatment (Nakano, Pinnow, Flaws, Sorkin, & Gallicchio, 2012). An anticipated 1.2 billion perimenopausal or postmenopausal women will be affected by hot flashes by 2030 (Lewis, 2009). Hormone therapy has been used to avert and/or treat the various health variations during perimenopause and subsequent to menopausal transition (Parke & Abernethy, 2008).

Physiology of Menopause

The average age for natural menopause in the US is 51 (NAMS, 2013). Menopause develops from the reduced secretion of the ovarian hormones estrogen and progesterone, which occurs as the number of ova present in the ovaries of a female precipitously decreases and declines during the reproductive years and the finite ovarian follicles are depleted (Nelson, 2008). The original balance among the hormones estrogen, progesterone, follicle stimulating hormone (FSH), and luteinizing hormone (LH) convert to a varying slightly estrogen and/or progesterone may begin to cycle at lower than usual levels, while FSH and/or LH levels may rise slightly higher to compensate, while cycling of the menses still continues (Wright & Leonard, 2010). With the onset of menopause, menstrual cycle lengths vary in irregularity, and the FSH concentrations rise in reaction to the decreased concentrations of ovarian hormones (Nelson, 2008). The cessation of menses and estrogen production is the finality of menopause.

Natural menopause follows 12 months of amenorrhea from the last menstrual period (North American Menopause Society (NAMS, 2007). Premature ovarian failure, known as early menopause, is the result of the cessation of ovarian function in women under the age of 45 (Holloway, 2011). The average American woman usually experiences menopause around age 51

(Morrow, Mattar, & Hortobagyi, 2011), however, this is determined by genetics, environmental factors such as smoking, and surgery (oophorectomy), chemotherapy or radiation therapy (Rees, Stevenson, Hope, Rozenburg, & Palacio, 2009). The menopausal age differs around the world and is described to be at age 48 in Mexico, 45.8 in Turkey, and age 49.3 in Korea (Melby et al., 2005).

The symptom of hot flashes is one of the well-known occurrences of menopause, which occurs in >75% of menopausal women and has a tendency to be most severe in the first two years of menopause (Nakano et al., 2012). Hot flashes occur with differing severity and frequency from anytime day or night, and can be complemented by sweating, tachycardia, palpitations, anxiety, irritability, and feelings of panic. Hot flashes can average up to four minutes and range in duration from a few seconds to ten minutes, while night sweats can be associated with hot flashes or occur independently (Hickey, Davis, & Sturdee, 2005). The physiological decline of estrogen as a result of menopause is correlated with increased risk for major health variations comprising of osteoporosis, cardiovascular disease (CVD), and diabetes, (Nelson, 2008; Shoupe, 2012).

Effects of Menopause

Osteoporosis

Osteoporosis is the most prevalent health variation as the hormonal influence of estrogen on bone health dissipates with the onset of menopause. The progressive changes in bone structure, quality and density lead to pathological fractures and an increase in morbidity and mortality among menopausal women (Christenson, Jiang, Kangan, & Schnatz, 2012). It is estimated that 13% to 18% of women in the United States, who are at least 50 years old, have osteoporosis, and an additional 37% to 50% have osteopenia, which is the presence of less than

the normal amount of bone mass. Osteoporosis causes one million fractures yearly, and the mortality rate following a hip fracture is 12% to 20%. Hip fractures in postmenopausal women is the second leading cause of admission to nursing homes and is one of the major disorders that contributes to the loss of independence and quality of life (NAMS, 2010).

Bone remodeling is a combined process of bone resorption followed by bone formation. Osteoclasts promote bone resorption at the cellular level by stimulating the production of acid and enzymes that dissolve bone mineral and proteins. The events occur when there is an imbalance between bone resorption and bone formation, thereby resulting in a decrease of bone mass and the increased risk of fracture from bone loss (NAMS, 2010).

Bone health is known to be influenced by several hormones regulating the process of bone resorption and formation, including the sex steroid hormones of testosterone and estrogen (Department of Health and Human Services (DHHS, 2004). Estrogen deficiency is associated with disease states such as Turner's syndrome, athletic amenorrhea or anorexia nervosa during this time, and is linked to low bone mass (Lindsay, 2004). Menopause is associated with increased rates of bone turnover and rapid spurts of bone loss from the decline of estrogen. The reduction in the estrogen receptors in bone is believed to be a primary factor in this large increase in bone resorption with reduced bone formation at menopause (DHHS, 2004). The addition of hormone therapy (HT) in women who are on average a decade past menopause (mean age of 63 years) preserves bone integrity, prevents bone loss and reduces the risk of fractures (DHHS, 2004).

Bone loss in older women may also be affected by the decreased dietary intake of calcium, vitamin D, and decreased physical activity, all of which contribute to maintaining bone health (NAMS, 2010). The amount of estrogen loss can affect the absorption of vitamin D and

calcium, which will then result in the interference of bone formation. Additionally, conditions affecting the absorption of food, including ulcerative colitis, Crohn's disease, gastric surgery, and liver disease contribute to the development of osteoporosis (Holloway, 2011). A menopausal woman with the following associated conditions is also at increased risk for osteoporosis: thin build, weight loss, anorexia, and low body mass index (Rees et al., 2009).

Diagnosis of Osteoporosis

Bone of the hip and spine is tested through densitometry also referred to as Bone Density Scan (DEXA). The measurement is represented by a T-score or a Z-score. The number reported represents the amount of bone in comparison to a young adult of the same gender with peak bone mass. A score above -1 is considered normal, while a score between -1 and -2.5 is classified as osteopenia (low bone mass), and an osteoporosis score is below -2.5. The T-score is used to estimate a woman's risk of developing a fracture, and a Z-score may indicate the need for further testing (Radiological Society of North America, 2014).

Bisphosphonates are deemed as first line therapy in the treatment of osteoporosis and reduce spine fractures by 40% to 70% and hip fractures by 20% to 35% (Christenson et al., 2012). Selective estrogen receptor modulators (SERMs), known as raloxifene (Evista), lasofoxifene and bazedoxifene, lower the risk of vertebral fractures in postmenopausal women (Archer et al., 2011). The current National Osteoporosis Foundation (NOF) guidelines state treatment with pharmacological agents should be considered in postmenopausal women aged ≥ 50 years who present with hip or vertebral fracture; T score ≤ -2.5 at the femoral neck, total hip, or spine post evaluation; or low bone mass and a 10-year probability of hip fracture $\geq 3\%$ or a 10 year probability of major osteoporosis related fracture $\geq 20\%$ based on the Fracture Risk Assessment Tool (FRAX) calculation (National Osteoporosis Foundation, 2008).

Another method for predicting bone loss is serum C-telopeptide (CTx) which is a reference bone marker for resorption. The CTX marker was found to be most sensitive and a better marker for bone mineral density (BMD) by Garnero, Sornay-Rendu, Duboeuf, and Delmas (1999). Bone turnover markers such as CTx were found to be useful and may assist in the prediction of menopausal women for osteoporosis (Garnero, 2008).

Landmark Studies Related to Osteoporosis

The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, the National Heart, Lung, and Blood Institute (NHLBI) and the National Institutes of Health (NIH) initiated a major clinical trial in 1987, known as the PEPI trial. The trial was conducted at seven clinical sites across the United States, and included 875 healthy postmenopausal women, ages 45-64, who were followed for three years. The women were predominately white, but included a variety of races, while a third had undergone a hysterectomy (The Writing Group for the PEPI Trial, 1996). The four hormone options in the PEPI trial were: 1) Premarin (conjugated equine estrogens CEE) only daily, 2) Premarin (CEE) and Progestin (medroxyprogesterone acetate), both daily, 3) Premarin (CEE) daily and synthetic Progestin 12 days per month; and 4) Premarin (CEE) daily and micronized progesterone 12 days per month; or 5) placebo.

In the PEPI trial women were evaluated for bone mineral density (BMD). Those assigned to the placebo group experienced a loss of 1.8% of spine BMD and 1.7% of hip BMD on the 36-month visit. Conversely, women with regimens increased their spinal BMD from 3.5% to 5.0% and experienced a 1.7% mean increase of BMD in the hip. The women assigned to estrogen (CEE) daily plus medroxyprogesterone had significant increases of 5% spinal BMD with average increase of 3.8% (Miller & Franklin, 1999).

The Danish Osteoporosis Prevention Study (DOPS) was a randomized controlled trial

that included 1006 younger women at the onset of menopause treated with oral estradiol and norethindrone acetate or estradiol alone for ten years, and who were followed for up to 16 years to assess osteoporosis. The findings of the study did not report any results related to osteoporosis outcomes (Schierbeck et al., 2012). Data from 2004-2005 revealed that age-adjusted osteoporosis-related fractures had risen, compared to 2000-2001 (Islam, Liu, Chines, & Hetzer, 2009) while an observational study of 80,955 women over 6.5 years, who had discontinued treatment, were found to have an increased rate of hip fractures compared to women that continued taking hormone treatment (Karim, Dell, Greene, Mack, Gallagher, & Hodis, 2011).

Results of Estrogen Loss

Insulin Resistance

Menopause can be considered a risk factor for CAD in women as a result of the potential effects of ovarian failure on cardiovascular function, blood pressure and the assorted metabolic parameters of glucose tolerance and lipid profiles. Prevention strategies for menopausal women should include the reduction of blood pressure, weight control and controlling glucose metabolism (International Menopause Society Writing Group (IMSWG), 2011).

The incidence of abdominal obesity is a known-risk factor for metabolic and cardiovascular diseases (Despres, Moorjani, Lupien, Tremblay, Nadeau, & Bouchard, 1990; Despres, 1993). The cause of menopause-transition effects with metabolic disease is unclear however the association may be related, to body fat distribution increased abdominal adipose tissue related to metabolic syndrome, involving type 2 diabetes, hypertension, and dyslipidemia (Despres, 1993; Despres et al., 1990; DeFronzo, 1997). Estrogen utilizes anti-diabetic measures by mechanisms that affect glucose homeostasis (Louet, LeMay, & Mauvais-Jarvis, 2004). The

reduction of peripheral insulin sensitivity, increased hepatic clearance of glucose and reduced pancreatic secretion of insulin in post-menopausal women has been described as the loss of estrogen may influence these alterations (Toth, Tchernof, Sites, & Poehlman, 2000).

Insulin Resistance Results in Landmark Studies

Clinical trials in postmenopausal women with estrogen (ET) and estrogen with progestin therapies (EPT) have given positive evidence for the promising effect of estrogen on glucose. The findings from a prospective randomized controlled PEPI trial found that all women receiving estrogen regimens had a reduction in fasting glucose levels, however blood glucose two hours after eating seemed to be elevated (The Writing Group for the PEPI Trial, 1996). The Heart and Estrogen Progesterone Replacement Study (HERS), the Women's Health Initiative, and the Kronos Early Estrogen Prevention Study (KEEPS) were randomized controlled clinical trials, revealing favorable benefits with estrogen therapy on glucose metabolism in postmenopausal women (Herrington et al., 2000; Kanaya et al., 2003; Margolis et al., 2004; & Lobo, 2013).

Clinical trials have shown the benefit of hormone replacement therapy has had favorable results on body composition, where a significant increase in fat mass and trunk fat has been reported in the control groups after five years (Norris, Joyce, O'Keefe, Sheppard, & Booner, 2002). Abdominal obesity research has been studied in menopausal women evaluating body mass index (BMI), waist circumference, fat-mass, lean mass and physical activity related to fat distribution. Results found that increases in visceral adiposity are associated with insulin resistance, hypertension, and hyperlipidemia, as seen in studies by (Despres, 1993, Despres et al., 1990; & Franklin, Ploutz-Snyder, & Kanaley, 2009).

The favorable outcome of the significant decrease for diabetes mellitus incidence in the

estrogen progesterone therapy group in the HERS and Women's Health Initiative (WHI) trials compared to the placebo group is undeniable (Kanaya et al., 2003; Margolis et al., 2004). These results support the function of estrogen progesterone therapy (EPT) in the prevention of DM in postmenopausal women, however beneficial, EPT in postmenopausal women is associated with greater rates of adverse events for heart attack, stroke (cardiovascular events) and breast cancer incidence, and is therefore not considered to be safe for the improvement of health in postmenopausal women (Rossouw et al., 2002).

Cardiovascular Disease

The four contributing risk factors: hyperlipidemia, hypertension, obesity, and diabetes are primarily nutritional in origin however these risk factors are associated with increased risk for developing cardiovascular disease (Franco, Cooper, Bilal, & Fuster, 2011). The incidence of cardiovascular disease (stroke, and coronary heart disease) is rare in women before menopause, but is the most common cause of death in women over the age of 60, while coronary heart disease is the single most common cause of death in women over age 60 (Brockie, 2008). The alterations caused by atherosclerotic changes to the coronary arteries, resulting in ischemic damage to the myocardium, presenting in women eight to ten years later than men (Schenck-Gustafsson, 2007).

The associated changes in lipid metabolism and higher levels of lipoprotein (a) linked with increased atheroma, changes in carbohydrate metabolism with increasing insulin resistance, hyperlipidemia, diabetes, hypertension, and obesity are associated with lower estrogen levels after menopause (Jackson, 2008). Additionally women with high C-reactive protein are at increased risk for cardiac and vascular events, with raised homocysteine levels (Brockie, 2008). Finally, the life-style risk factors associated with the increased risk for coronary heart disease are

smoking, stress and depression (Jackson, 2008).

Cardiovascular Disease and Landmark Studies

The PEPI trial followed 875 healthy, post-menopausal, predominately white women, ages 45-64 for three years. The goal was to see the effects of various hormone regimens on the key risk factors for heart disease. The initial results revealed estrogen-only therapy raised the level of good high density lipoprotein (HDL); insulin levels were not affected with any of the hormone regimens; and all of the hormone regimens caused an increase in triglyceride levels.

Uncertainties regarding hormone replacement therapy and their effects of how long and at what age a woman should start hormone therapy, reducing heart attacks and strokes was one of the outcomes from the PEPI trial (The Writing Group for the PEPI Trial, 1996).

The initial results of the WHI and the coronary findings were of borderline significance 1.24 (1.00-1.54) (Manson et al., 2003). The findings of the WHI were varied according to Stevenson, Hodis, Pickar, and Lobo (2009). In a study by Weinberg, Young, Hunter, Agrawal, Mao, and Budoff (2012), of the WHI, coronary calcium scores were significantly reduced in women taking estrogen, thereby leading to a statistically significant reduction in coronary disease. The sub-analyses of large randomized trials are suggestive of coronary benefits in younger menopausal woman receiving estrogen therapy however this should be interpreted with caution (Lobo, 2013).

Looking at the WHI 10 years later, a follow-up-of women in the estrogen-alone trial revealed that women aged 50 to 59 years had a significantly reduced rate of myocardial infarction (MI) and coronary heart disease (CHD), and a 30% reduction in all-cause mortality (LaCroix, Chlebowski, & Manson, 2011). The hypothesis of “timing” recommends younger symptomatic women at the onset of menopause may be protected from CHD, where an older

group of women, who were treated initially, may experience early harm. Lastly women who were older and treated for the first time with estrogen may have no benefit from HT (Lobo, 2013).

Stroke

Hormone therapy and the effects of stroke are controversial, because of the numerous variables confounding the data (obesity and hypertension) and the risk of marginal significance that exists (Lobo, 2013). Ischemic stroke (not hemorrhagic stroke) has shown a small increase in younger women receiving standard doses of oral estrogen by approximately 30% in observational data. Women have a reduced rate of stroke incidence compared to men up until the age of 85 years or older. The incidence for ischemic stroke in women age 55 to 65 years old is three in 1000, however the risk nearly double during the menopausal transition period and continues to increase with age (Bushnell, 2009). The mechanism for the increased risk of ischemic stroke in the younger menopausal woman is thrombotic and not atherosclerotic as in older women and may be in origin of thrombophilic sensitivities (Sare, Gray, & Bath, 2009).

Stroke was reported in the WHI clinical trial results revealing an overall increase in the menopausal group that received Estrogen CEE + MPA, and an increased risk was less evident in the younger menopausal group of women (Rossouw et al., 2007). The risk for stroke in women nearly doubles between the ages of 55 and 65 years, which is consistent with at least 10 years after the age of menopause (Bushnell, 2009). There are only a few studies examining the association between age at menopause and stroke (Jacobsen, Heuch, & Kvale, 2004; de Lecinana, Egido, & Fernandez, 2007; Hu, Grodstein, & Nennekens, 1999).

Venous Thrombosis

The relevancy of ischemic stroke in menopausal women who use hormone therapy is

related to the findings of venous thrombosis risk. In the WHI (Rossouw et al., 2002), the risk for venous thromboembolism with standard doses of oral estrogen was found to have increased by 33% with a more than two-fold increase, with most incidences occurring within the first two years of therapy; while the addition of micronized progesterone the risk increased to 59% compared with conjugated equine estrogen (CEE) alone and no mortality changes were reported (Curb et al., 2006). The estrogen-alone trial of the WHI revealed a more obese cohort, with numerous women in this group having had a hysterectomy and previous exposure to hormones (Rossouw et al., 2002).

The use of oral estrogen increases the risk for thrombosis. Standard doses of oral estrogen increase the risk of venous thromboembolism approximately two-fold, as was observed in the WHI trial (Rossouw et al., 2002). Most cases were reported in the first or second year of therapy, with no changes in mortality (Lobo, 2013). The use of transdermal estrogen is not associated with an increased risk for thrombotic events (Olie et al., 2011). Researchers have steadily revealed a twofold increase in the risk for venous thromboembolism (VTE) with HRT use (Cushman, Kuller, & Prentice, 2004; Canonico, Oger, & Plu-Bureau, 2007).

Breast Cancer

The fear women experience in regards to hormone therapy (HT) is the potential for developing breast cancer (Walsh-Childers, Edwards, & Grobmyer, 2011). The incidence for breast cancer among women utilizing estrogen was initially described by Hoover, Gray, Cole, and MacMahon (1976). In a case-controlled study by Ross et al., (1980), 138 women with breast cancer were reported and the risk ratio for cumulative estrogen doses larger than 1500 mg versus no hormone therapy was 2.5. Pike, 1983 and Bergkvist, Adami, Persson, Bergstrom, and Krusemo (1989) found a small increased risk of breast cancer related to hormone therapy with

longer durations of their use, compared to no hormone therapy.

In 1995, the prospective Nurse's Health Study (established in 1976) was published to quantify the relationship between the use of hormones and the risk for breast cancer in postmenopausal women. The researchers confirmed there was a greater risk for increased breast cancer incidence among older women taking hormones after menopause and a stronger risk was seen with five or more years of hormone use, specifically among women using estrogen plus progestins. Colditz et al., found the risk for estrogen alone increased the risk for breast cancer (1995).

In another study, a Collaborative Group on Hormonal Factors in Breast Cancer in 1997 consolidated data from previous case-controlled studies of 52,705 women. Women with breast cancer and 108,411 control subjects revealed a significant increase for the risk of breast cancer and the increased risk was associated with the duration of estrogen use (Chlebowski & Anderson, 2012). There are many issues one must consider when assessing a woman's risk of developing breast cancer with HRT use. Age is an important risk factor and most studies report an increased risk in older women (Parke & Abernethy, 2008).

The Million Women Study, a population-based cohort study of women between the ages of 50-64, was completed in the United Kingdom. 800,000 women were recruited with 33% who were utilizing HRT currently while there were 47% that had used HRT at some time in the past (Banks, Beral, & Reeves, 1999). The main purpose of the study was to examine the relationship between breast cancer and the use of HRT. As one of the largest studies ever conducted, the findings yielded higher breast cancer mortality for women who were diagnosed with breast cancer while using estrogen plus progestin compared to the non-hormone therapy group (Beral, 2003).

The WHI reported a significant increase of 26% in the relative risk in duration effect for invasive breast cancer in women between the ages of 50-79 years old with the treatment of oral conjugated equine estrogens (CEE) plus medroxyprogesterone acetate, versus the placebo group in the study (Stevenson et al., 2009). Later, in a subgroup analysis, the initial increased risk of breast cancer was only seen in those who had used HRT before entering the study, suggesting that up to four years of exposure to combined HRT did not lead to an increased risk for breast cancer, while the type and dose of progestin and estrogen may affect the risk for breast cancer (Hickey et al., 2005).

Hormone Replacement Therapy

Hormone replacement therapy, and/or menopausal hormone therapy (MHT), are medications that combine the hormones estrogen and progestin (synthetic forms of progesterone), and on occasion, are used with testosterone (Garad, Burger, & Davison, 2011). Oral estrogen preparations include: conjugated equine estrogens (CEE), synthetically derived piperazine estrone sulphate, estriol, micronized estradiol, and estradiol valerate (Hickey et al., 2005). Other forms of HRT include: estradiol in a patch, gel, a slow-release percutaneous implant, or nasal spray. There are also intravaginal forms of estrogens that include rings, creams, topical, tablets, and pessaries (Smith & Wein, 2010).

Hormone replacement therapy has been utilized as the initial line of treatment for the relief of menopausal symptoms (Buist et al., 2004). The increasing life expectancy among women, and the incidence of osteoporosis and cardiovascular disease justified the popularity of HRT prescribed for symptom relief and chronic disease prevention that was seen in the 1990's (Garard et al., 2011). Hormone replacement therapy has been used to prevent or treat the numerous health alterations of erratic or excessive vaginal bleeding, vasomotor symptoms of

night sweats and hot flashes associated with menopause (North American Menopause Society (NAMS, 2005).

Between 1999 and 2000, 38.3% of women age 50-59 utilized HRT. A decade later (2000-2010) in the same age group, only 6.7% reported taking HRT, while currently, 4.7% of women over 40 seek HRT (Sprague, Trentham-Dietz, & Cronin, 2012). The reported drop in hormone therapy was linked to the results of the WHI, 2002 and physicians discontinuing HRT in menopause women (Endocrine Society, 2006). The Food and Drug Administration (FDA) requires manufacturers of FDA-approved estrogen and progesterone products to use class labeling, also known as black box warning, indicating a drug with special problems, particularly possibly leading to death or serious injury subsequent to the results of the WHI (U.S. Food and Drug Administration (USFDA), 2008). While on the tenth anniversary of the WHI 2002 trial, the consistent theme exists much has been learned and yet the experts “don’t agree” regarding the safety and efficacy of HT from previous and ongoing studies to date (Stuenkel et al., 2012).

Controversies Related to Compounded Bioidentical Hormones

The U. S. Food and Drug Administration (FDA) responded to a citizen’s petition in 2005 on behalf of Wyeth Pharmaceutical. The petition filed by Wyeth was against the manufacturing and marketing of compounded BHRT (USFDA, 2008). Wyeth produces the drug Premarin which is a conjugated estrogen and other contraceptives (Wyeth, 2014). The drug (Premarin) was associated with negatives outcomes from the WHI, HERS, and PEPI trials (Rossouw et al., 2002). Subsequently, the FDA warned against the inclusion of estriol in compounded preparations, and issued warning letters to nine compounding pharmacies in the United States following the Wyeth petition (USFDA, 2008).

The compounding of medications continued, until an incident lead to the deaths of 25

patients and 344 patients diagnosed with fungal meningitis due to the contamination of a batch of injectable medication produced by the New England Compounding Center (NECC) in Framingham, Massachusetts (Savage, 2012). This led to the scrutinized practice of compounding (Savage, 2012). The Centers for Disease Control and the U.S. Food and Drug Administration (FDA) confirmed the incidence of a fungus in unopened vials of preservative-free methylprednisolone acetate from one of the three implicated lots from the NECC, furthermore laboratory confirmation linked the outbreak of fungal meningitis (Food and Drug Administration (FDA), 2012).

Subsequently, the FDA instituted a new law in November 2013, enacting the Drug Quality and Security Act (HR 3204), signed by President Barak Obama, the compounding track-and-trace legislation. This law has impacts to compounding pharmacies such as voluntary elect to be “outsourcing facilities” regulated by state boards of pharmacy and the FDA. The FDA has to determine how the implementation of the regulatory process will occur, while traditional pharmacies and compounding pharmacies will continue to be regulated by state boards of pharmacy (Yap, 2014).

Current Recommendations for Menopause Symptoms

The American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine Practice Committee recommend that women be counseled on menopausal therapies proven to be safe and effective by the FDA. Physicians should practice caution in prescribing compounded hormones when FDA-approved alternatives exist. The following FDA approved products include Estradiol (transdermal or oral, micronized), Estrone (active ingredient in conjugated equine estrogen preparations), and progesterone (oral, micronized or vaginal gel or insert) (American College of Obstetricians and Gynecologists (ACOG), 2012).

The US Preventive Services Task Force (USPSTF) recommended against the use of estrogen alone and combined estrogen and progestin for the primary prevention of chronic conditions in postmenopausal women (2012). However, the USPSTF did not examine the data related to the use of hormone therapy for the treatment of women with menopausal symptoms of hot flashes or vaginal dryness. Additionally, the USPSTF recommendations are not relevant to women younger than 50 years of age who have undergone surgical menopause (2012).

The findings from the WHI trial reported new information regarding the age of the participants and the time from menopause to initiating hormone replacement therapy. This has now become relevant to the outcomes initially reported. The recently updated information revealed the study group was an older population and therefore this may have changed the outcomes of the WHI study (Lobo, 2013). While on the tenth anniversary of the WHI 2002 trial, the consistent theme exists that much has been learned and yet, the experts “don’t agree” regarding the safety and efficacy of HT from previous and ongoing studies to date (Stuenkel et al., 2012).

Bioidentical Hormone Studies

Bioidentical hormone trials include a randomized blinded four-arm 16-day clinical trial of forty postmenopausal women that were assigned to one of three different doses of a compounded estrogen cream known as Bi-est, + compounded oral progesterone, or a conventional estradiol patch such as Vivelle-Dot + Prometrium (Sood et al., 2013). The goal of the researchers was to compare the pharmacokinetics of conventional and compounded hormone preparations. All study medications were prepared and dispensed by the same compounding pharmacist, thereby minimizing variability in the compounding medications. The absorption patterns with Biest creams were found to be highly variable and no peak absorption was

observed, while the small increments in estradiol levels with low-dose Biest formulations raised the question of how much symptomatic benefit is credited to doses derived from a placebo effect. The findings raised a question as to whether the compounded formulation doses are sufficient to provide any bone benefits in menopausal women (Sood et al., 2013).

An observational cohort study of women, between the ages of 18-89, who received a compounded BHRT product from January 1, 2003 to April 30, 2010, from six community pharmacies was conducted. The data included patient demographics, comorbidities, therapeutic outcomes, and hormone therapies, women self-rated menopausal symptoms, and descriptive statistics were used to characterize the data and adverse events. The study included 296 women who received BHRT from Oakdell Pharmacy with a mean age of 52. Reported results included a 25% decrease in irritability and 22% reduction in anxiety within three to six months of treatment. Bioidentical hormone replacement safety from this cohort of women had documented follow-up for 1.9 years regarding MI and breast cancer, with no women experiencing MI or breast cancer. While the results are promising, larger studies of women need to be conducted for a longer period of time to examine the impact of BHRT on vasomotor symptoms, MI, and breast cancer (Ruiz et al., 2011).

The review of the literature includes relevant research that has led to the related project. Research regarding the safety of BHT is sparse; some of the existent literature focuses on the pharmacodynamics and therapeutic reports for relief of symptoms over short time periods. Therefore the need to research the topic of safety of BHT is requisite.

Problem Statement and Research Question

The review of the literature reveals BHRT for the treatment of menopause symptoms has benefits for the improvement of symptoms however the lack of safety data is a concern

(Cirigliano, 2007). Limitations with the current research include the lack of clinical studies with the use of Biest (Estriol and Estradiol), and Triest (Estriol, Estradiol, and Estrone) with or without Progesterone. No studies state the safety for the use of BHRT. The purpose of this project was to investigate if the use of Biest and Progesterone after four years or longer increased the risk for osteoporosis, breast cancer and cardiovascular disease.

Chapter 3

Methods

Project Design

A cohort retrospective descriptive chart review was utilized for this study. The study included menopausal women that utilized BHRT specifically Biest and Progesterone for four or more years. A retrospective study design utilizes existing data, and for this project served as a useful purpose to evaluate BHRT use over a time period of four or more years.

Setting

The setting was a conducted in a practice that prescribed and treated women with BHRT. The practice was in existence for thirteen years, and had three physicians, one naturopath, and one nurse practitioner, each prescribing BHRT when indicated. The practice did not accept medical insurance and required payment at the time services were rendered. The practice was located in Southern California and has a Northern California office location, however for the purpose of the study only the Southern California office was utilized.

Sample

The population was identified by the Compounder Four System (Compounder 4), a computerized system for prescriptions in the dispensary at Southern California private practice. The population was menopausal women between the ages of 40 and 70, who were prescribed and utilized BHRT. The Compounder Four System generated a list of women seen in the practice

who met criteria from January 2008 to October 2014. The population consisted of women who were able to pay for services at the time of their visit. The office did not collect data on racial background or demographic data, thus this information was excluded.

Instrumentation

There was one survey tool utilized for the study. A 20 question tool was developed based on the initial patient questionnaire from the practice setting, and subsequently additional information was added to determine if incidences for osteoporosis, breast cancer, or MI had occurred, based upon the literature reviewed. See Appendix A for the tool. The physician director of the practice provided written consent for the study to be conducted in his office. The original document was revised for the study and verbal consent was given for the use of questions from the initial patient questionnaire. Since the revised tool was not utilized in previous studies and was not tested for reliability, it was piloted during the study.

Data Collection

A chart review was conducted once the inclusion criteria were met for women who used Biest and Progesterone for four years or longer. The patients were identified utilizing the Compounder Four (Compounder 4) compounding system used in the dispensary of the Southern California private practice where the study was conducted. A list was generated from the Compounder Four system and charts were reviewed from those individuals meeting inclusion criteria. A chart review was then conducted once the inclusion criteria was met by the primary investigator to verify that inclusion criteria had been met for continuous Biest and Progesterone use for four or more years, utilizing the Compounder four system and pharmacy renewal verification from the subjects chart. The developed tool and a tool for each patient's chart were utilized to maintain accurate data collection. Basic demographic data without patient identifiers were also part of the data collected.

Data Collection Procedures

Data was coded (de-identified). Each chart identified by the Compounder Four System was reviewed by the primary investigator for inclusion criteria. Once the chart and data from the Compounder Four System had been verified the chart review tool was used and data was then collected. Once data was collected data was then entered into an excel file with de-identified information. Data was stored in a locked filing cabinet in the primary investigator's main place of employment, where it will be kept for five years.

Data Analysis

The primary investigator utilized Statistical Package for the Social Sciences (SPSS), version 22. Data was analyzed and data sets were created with the assistance of a statistician. The data collected was quantitative and categorical data, therefore a t-test and paired t-tests were used as statistical tests as part of the data analysis. Additionally, means, standard deviations, and correlations were part of the analysis. Lastly, correlations were completed to measure association or relationship between BHRT and outcomes.

Ethical Considerations

The study was submitted to the institutional review board (IRB) at Fresno State University, with permission to conduct the study granted by the Medical Director and owner of the private practice. It was determined to be exempt from further IRB review due to the low risk nature of the study. This was a retrospective chart review therefore health information was collected so anonymity was assured. The investigator did not know or treat the majority of the subjects that were identified for inclusion criteria for the chart review therefore the data collected should have no affected bias.

Chapter 4

Results

Demographics

There were sixteen descriptive variables surveyed on the tool see Appendix A. The mean age was 60.13 (SD = 5.02); the mean pre-treatment body weight was 156.28 pounds, and post treatment mean body weight of 156.27 pounds. Table 1 presents the marital status for the women with the majority of patients married (78.6%). The medications reported on initial visit and post Biest and Progesterone treatment is in Table 3.

Table 1
Marital Status (N = 101)

Demographic	n	%
Marital Status		
Married	78	78.6%
Divorced	8	8.2%
Single	7	7.1%
Separated	3	3.1%
Widowed	2	2.0%

The reported symptoms of menopause for the women seeking treatment during the initial visit are labeled in Table 2. One patient did not list any reported symptoms therefore the table represents symptoms from 100 patients. The most reported symptoms were fatigue, poor sleep and hot flashes.

Table 2
Reported Symptoms at Initial Visit (N =100)

Symptoms	n	%
Fatigue	45	45%
Poor Sleep	41	41%

Hot Flashes/Night Sweats	35	35%
Weight Gain	32	32%
Mood Swings/PMS	29	29%
Low Libido	22	22%
Depression	20	20%
Brain Fog/Poor Memory	20	20%
Painful Intercourse/ Vaginal Dryness	19	19%
Headaches/Migraines	12	12%
Anxiety	8	8%
Frequent Urination/ Urinary Incontinence	8	8%

Table 3 presents the medications by classification utilized by the women as reported during their initial visit and post BHRT treatment. There were 54 women that were using HRT/BCP and 31 women taking thyroid medication, while post BHRT treatment the HRT/BCP decreased to zero and the use of thyroid medication increased to 77 women.

Table 3

Medications on Initial Visit and Post BHRT Treatment (N=101)

Medications/Classifications	<i>Pre-Initial</i>		<i>Post- Biest and Progesterone</i>	
	n	%	n	%
HRT/BCP	54	53.4%	0	0
Thyroid	31	30.69%	77	76.2%
Depression	22	21.78%	14	13.86%
Anti-hypertensives	20	19.8%	20	19.8%
GI	13	12.87%	9	8.9%
Allergy/Asthma	13	12.87%	11	10.89%
Anti-anxiety	11	10.89%	9	8.91%
Pain non-narcotic/migraine	11	10.89%	5	4.95%
Sleep aids	8	7.9%	5	4.95%
Pain-narcotic	6	5.94%	5	4.95%
Antidiabetic	4	3.96%	7	6.9%
Lipid lowering	4	3.96%	4	3.96%
Weight loss	4	3.96%	9	8.91%

NSAID	4	3.96%	5	4.95%
ASA	4	3.96%	3	2.97%
Biophosphonate	3	2.97%	3	2.97%
Seizure	1	0.99%	1	0.99%
ADHD	1	0.99%	4	3.96%
BHRT	0	0	101	100%

Table 4 identifies the total number of women with menopause induced surgeries, therefore the physiological decline of estrogen as a result of menopause is correlated with increased risk for major health variations comprising of osteoporosis, cardiovascular disease (CVD), and diabetes, (Nelson, 2008; Shoupe, 2012). As presented in Table 4, total charts reviewed found 26 women with a surgical-induced menopause.

Table 4

Menopause-Induced Surgeries (N =26)

Menopause-Induced Surgeries	<i>n</i>	%
Partial Hysterectomy	15	15.15%
Total Hysterectomy	11	11.1%

Cardiac

Table 5 is representative of blood pressure data for the women upon initial visit and during the last office visit utilizing the eighth Joint National Committee guidelines (JNC 8) for hypertension. The blood pressure data is limited to initial visit and last visit therefore lacking blood pressure data to adequately make a diagnosis of hypertension because of deficiencies of three consecutive blood pressure readings, lack of health history, and ethnicity according to the nine recommendations for instituting treatment in the JNC 8 guidelines (James et al., 2014).

Table 5

Blood Pressure on Initial Visit (N = 100) and Last Visit (N = 96)

B/P	<i>Initial Visit</i> <i>n = 100</i>		<i>Post BHRT</i> <i>n = 96</i>	
	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>
<u>85 - 98</u> 56 - 63	3	3%	2	1.92%
<u>100 - 139</u> 56 - 88	78	78%	64	61.44%
<u>140 - 184</u> 90 - 113	19	19%	30	28.79%

The family history for cardiac incident before the age 55 was found in twenty-five fathers. Forty-three of 101 (N) reported cardiac incidence of which 25 (24.8%) were fathers, who had known history for a cardiac event see Table 6.

Table 6

Family History for Cardiac Incident (N = 43)

Family History	<i>n</i>	<i>%</i>
Father	25	24.8%
Mother	11	10.9%
Brother	4	4.0%
Sister	2	2.0%
Grandfather	1	1.0%

Table 7 categorizes the type of cardiac incident experienced by the women pre-treatment and post BHRT treatment with compounded prescription use. There were 23 women with a documented cardiac incident prior to starting treatment with Biest and Progesterone compounded treatment: eight of the women with a history of existing hypertension, one woman with a myocardial infarction, one with atrial fibrillation, one with hyperlipidemia, one woman with an irregular heart valve and one with mitral regurgitation see Table 7. The existing cardiac findings

may perhaps lead to possible myocardial infarction.

Table 7

Cardiac Incidence Initial Visit and Post BHRT Treatment (N = 23)

Initial Visit Cardiac Incidence	n	%
Cardiac Incidence Pre		
HTN	8	18.6%
Atrial Fib	1	2.3%
Myocardial Infarction	1	2.3%
Borderline HTN	1	2.3%
HTN/Hyperlipidemia	1	2.3%
Hyperlipidemia	1	2.3%
Irregular Valve	1	2.3%
Mild Mitral Regurgitation	1	2.3%
Mitral Valve Prolapse	1	2.3%
Phlebitis	1	2.3%
S-Tach	1	2.3%
Post BHRT		
Cardiac Incidence		
Atrial Fib	2	4.6%
HTN	2	4.6%
Hyperlipidemia	1	2.3%
Myocardial		
Infarction/Stroke	0	0%

Descriptive Statistics

Table 8 represents the initial and post Progesterone dosage levels for the women ranging from 25 milligrams to 400 milligrams. The 23 women initially taking 100 milligrams of Progesterone decreased to 15, while the women taking 200 milligrams of Progesterone was 64 women initially and increased to 71 at the four year visit. The most commonly used dosage of Progesterone was 200 milligrams in the patients.

Table 8

Initial and Post Frequency and Percent of Progesterone Compounded Dosage (N=101)

Dose	<i>Initial</i>		<i>Post</i>	
	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>
25-100mg	1	1.0%	0	0
50mg	1	1.0%	1	1.0%
50-100mg	1	1.0%	0	0
50-200mg	4	4.0%	0	0
100mg	23	22.8%	15	15.3%
150mg	5	5.0%	8	8.2%
100-200mg	1	1.0%	1	1.0%
200mg	64	63.4%	71	72.4%
300mg	0	0	1	1.0%
400mg	1	1.0%	1	1.0%

Screening for osteoporosis on initial visit, 40 (39.6%) women were screened for bone density and or c-telopeptide, while post BHRT treatment compounded prescription use, 43 (42.5%) women were screened for bone density or c-telopeptide. Similarly, screening for breast cancer, 11 (10.8%) women on initial visit had documented mammography results, while 23 (22.7%) women post Biest and Progesterone compounded prescription patients had documented mammography results. Twenty-five percent of post BHRT prescription treatment use in women was negative for breast cancer upon mammography screening, while the remaining patients self-reported negative results. Cardiac incident findings on initial visit revealed seventeen (16.8%) women reported had a previous cardiac history while, five (4.9%) women post BHRT compounded prescription use had reported a cardiac incident, and no myocardial infarctions were reported refer to Table 7.

The Biest medication route of preferred administration method on initial visit and post last visit is detailed in Table 9, with 88 women on initial visit that were prescribed a gel based Biest. Subsequently on the last visit the Biest method of administration increased to 90 women, while cream was not as commonly utilized.

Table 9

Initial and Post Method of Biest Administration (N = 101)

Method	<i>Initial</i>		<i>Post</i>	
	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>
Cream	12	11.9%	7	6.9%
Gel	88	87.1%	90	89.1%
Gel / Cream	1	1.0%	4	4.0%

Inferential Statistics

A paired samples *t*-test was conducted to determine the difference between pre BHRT and post BHRT for bone density. There were 29 patients with bone density data collected both prior to treatment and post BHRT treatment, a paired samples *t*-test indicated no significant difference between previous to BHRT treatment on bone density ($M = 403.55$, $SD = 236.14$) and post BHRT treatment bone density levels ($M = 367.10$, $SD = 191.74$) see Table 10.

Table 10

Mean, Standard Deviation, and Standard Error for Bone Density (N = 29)

Bone Density	<i>M</i>	<i>SD</i>	<i>SE</i>
Previous to BHRT	403.55	236.14	43.85
Post-test BHRT	367.10	191.74	35.61

Bone density did not significantly decrease after treatment, while there was a significant correlation between pre BHRT and post BHRT treatment and bone density: $r(29) = .568$, $p = .001$ as shown in Table 11.

Table 11

Paired Samples t-test Comparison of Pre and Post BHRT Treatment on Bone Density

($N = 29$)

	Dif. Of Means	<i>SD</i>	<i>r</i>	<i>t</i>	<i>df</i>	Sig. (2-tailed)
Pre – Post	36.45	198.70	.586	.988	28	.332

A paired samples *t*-test was conducted to determine the difference between pre BHRT and post BHRT treatment use on total cholesterol. For the 58 patients where total cholesterol data was collected both pre and post compounded prescription of BHRT treatment use, a paired samples *t*-test indicated no significant difference between pre Biest and Progesterone total cholesterol ($M = 205.26$, $SD = 40.00$) and post BHRT prescription use on total cholesterol ($M = 201.19$, $SD = 34.74$), $t(57) = .808$, $p = .422$ refer to Table 12.

Table 12

Mean, Standard Deviation, and Standard Error for Total Cholesterol (N = 58)

Total Cholesterol	<i>M</i>	<i>SD</i>	<i>SE</i>
Previous to BHRT	205.26	40.00	5.25
Post test	201.19	34.74	4.56

Total cholesterol levels did not significantly decrease after treatment. There was a significant correlation between pre Biest and Progesterone and post BHRT medication use on total cholesterol: $r(58) = .481$, $p < .001$ see Table 13.

Table 13

*Paired Samples t-test Comparison of Pre and Post BHRT Treatment on Total Cholesterol**(N = 58)*

	Dif. Of Means	SD	<i>r</i>	<i>t</i>	<i>df</i>	Sig. (2-tailed)
Pre – Post	4.07	38.34	.481	.808	57	.442

A paired samples *t*-test was conducted to determine the difference between pre BHRT and post BHRT prescription use on HDL cholesterol. For the 57 patients where HDL cholesterol data was collected both pre BHRT and post prescription of BHRT, a paired samples *t*-test indicated no significant difference between pre BHRT on HDL levels ($M = 67.33$, $SD = 20.25$) and post BHRT on HDL cholesterol levels ($M = 68.70$, $SD = 18.46$), $t(56) = -.777$, $p = .441$ see Table 14.

Table 14

Mean, Standard Deviation, and Standard Error for HDL Cholesterol (N = 57)

HDL Cholesterol	<i>M</i>	<i>SD</i>	<i>SE</i>
Previous to BHRT	67.33	20.25	2.68
Post test	68.70	18.46	2.44

HDL cholesterol levels did not significantly increase after treatment. There was a significant correlation between pre BHRT prescription use and post BHRT prescription use on HDL cholesterol: $r(57) = .768$, $p < .001$ see Table 15.

Table 15

Paired Samples t-test Comparison of Pre and Post BHRT Treatment on HDL cholesterol

($N = 57$)

	Dif. Of Means	<i>SD</i>	<i>r</i>	<i>t</i>	<i>df</i>	Sig. (2-tailed)
Pre – Post	-1.37	13.30	.768	-.777	56	.441

A paired samples *t*-test was conducted to determine the difference between pre BHRT and post BHRT on LDL cholesterol levels. For the 58 patients where LDL cholesterol data was collected both pre and post compounded prescription of BHRT, a paired samples *t*-test indicated no significant difference between pre BHRT LDL cholesterol levels ($M = 116.83$, $SD = 33.64$) and post BHRT on LDL cholesterol levels ($M = 113.88$, $SD = 29.73$), $t(57) = .653$, $p = .517$ refer to Table 16.

Table 16

Mean, Standard Deviation, and Standard Error for LDL Cholesterol (N = 58)

LDL Cholesterol	<i>M</i>	<i>SD</i>	<i>SE</i>
Pre test	116.83	33.64	4.42
Post test	113.88	29.73	3.90

LDL cholesterol levels did not significantly decrease after treatment. There was a significant correlation between pre BHRT and post BHRT levels of LDL cholesterol: $r(58) = .416$, $p = .001$ see Table 17.

Table 17

Paired Samples t-test Comparison of Pre and Post BHRT on LDL cholesterol (N = 58)

	Dif. Of Means	SD	r	t	df	Sig. (2-tailed)
Pre – Post	2.95	34.41	.416	.653	57	.517

A paired samples *t*-test was conducted to determine the difference between pre Biest and Progesterone and post BHRT on Triglyceride levels. The 57 patients with Triglyceride data was collected both pre and post compounded prescription use of BHRT, a paired samples *t*-test indicated no significant difference between pre Biest and Progesterone Triglyceride levels ($M = 105.93$, $SD = 59.71$) and post BHRT Triglyceride levels ($M = 97.42$, $SD = 44.93$), $t(56) = 1.517$, $p = .135$ seen in Table 18.

Table 18

Mean, Standard Deviation, and Standard Error for Triglyceride (N = 57)

Triglyceride	M	SD	SE
Previous to BHRT test	105.93	59.74	7.91
Post test	94.42	44.93	5.95

Triglyceride levels did not significantly decrease after treatment. There was a significant correlation between pre Biest and Progesterone and post BHRT levels of Triglyceride: $r(57) = .707$, $p < .001$ see Table 19.

Table 19

Paired Samples t-test Comparison of Pre and Post BHRT on Triglyceride Levels

($N = 57$)

	Dif. Of Means	<i>SD</i>	<i>r</i>	<i>t</i>	<i>df</i>	Sig. (2-tailed)
Pre – Post	8.51	42.34	.707	1.517	56	.135

An independent samples *t*-test was conducted to determine the difference on triglycerides level between Biest dosage after four years of compounded prescription use. Using the equality of variances correction, an independent samples *t*-test indicated a significant difference between triglyceride level between two/two compounded prescription dosage ($M = 73.13$, $SD = 19.35$) and two/four compounded prescription dosage ($M = 113.52$, $SD = 53.03$), $t(35) = -3.221$, $p = .003$ see Table 20.

Table 20

Mean, Standard Deviation, and Standard Error for Triglyceride Level ($N = 37$)

Dose	<i>n</i>	<i>M</i>	<i>SD</i>	<i>SE</i>
Two/Two	16	73.13	19.35	4.84
Two/Four	21	113.52	53.03	11.57

An independent samples *t*-test was conducted to determine the difference on HDL cholesterol level between progesterone dosages after four years of prescription use. An independent samples *t*-test indicated a significant difference between HDL cholesterol level between 100 milligrams prescription ($M = 101.75$, $SD = 28.86$) and 200 milligrams prescription ($M = 67.20$, $SD = 17.99$), $t(48) = 3.517$, $p = .001$ refer to Table 21.

Table 21

Mean, Standard Deviation, and Standard Error for HDL Cholesterol Level (N = 50)

Dose	<i>n</i>	<i>M</i>	<i>SD</i>	<i>SE</i>
100 milligrams	4	101.75	28.86	14.43
200 milligrams	46	67.20	17.99	2.65

A Pearson correlation was conducted to determine the relationship between pre progesterone level, post progesterone level, weight, age, post total cholesterol, post HDL cholesterol, and post LDL cholesterol. There was a significant negative relationship between post progesterone dosage and post HDL cholesterol levels: $r(58) = -.289$, $p = .028$, $r^2 = .08$, as progesterone level increased, post HDL cholesterol decreased.

There was no significant difference between post routes of administration (cream or gel) for post total cholesterol; post HDL, post LDL, post triglyceride, post bone density, age, or weight. Additionally there was no other significance between dose on post total cholesterol, post LDL, post triglyceride, post bone density, age, or weight. There were significant correlations noted for the paired samples t test; the only other significant correlation was post progesterone level and post HDL cholesterol.

Chapter 5

Discussion

A retrospective chart review was conducted on 101 charts from a Southern California private practice. All women who had utilized Biest and Progesterone for four or more years were included. The purpose of the project was to evaluate retrospectively if Biest and Progesterone compounded prescription use in women after four or more years increased the risk for osteoporosis, breast cancer and cardiovascular disease. The population was predominately

Caucasian and married. Their body weight stayed consistent with pre-treatment and post-treatment regimen. Only one patient reported no initial symptoms before seeking bioidentical hormone replacement treatment, while the remainder of the women disclosed symptoms of fatigue, poor sleep, hot flashes, and weight gain. Additional symptoms reported, but not as significant, included: depression, painful intercourse, brain fog, anxiety, frequent urination/urinary incontinence, hair thinning, and migraine/headaches.

Of the 101 women, 31 utilized thyroid medications and 54 women used birth control or hormone replacement therapy prior to being prescribed Biest and Progesterone. There were 20 women taking antihypertensive agents, four on antidiabetic medications, and four utilizing lipid-lowering agents, therefore past medical history would have revealed valuable information about the population.

The blood pressure on initial visit found 19 women were in the hypertensive category utilizing the Eighth Joint National Committee Guidelines, while at the four year mark there were 30 women whose blood pressure was in the 140/90 – 184/113 hypertensive category. Frequently used medications included: non-steroidal anti-inflammatory, narcotic pain and non-narcotic pain medications. While less commonly used medications were: allergy asthma medications and biophosphonates prior to Biest and Progesterone compounded prescription use. The use of sleep medications was found in eight patient charts: 11 women were utilizing anti-anxiety medication one patient was on a seizure medication, five women were utilizing antivirals, two were receiving treatment with antifungals, three patients were being treated with antibiotics and one patient was being treated with an attention deficit hyperactivity disorder medication. The patient population seen in the practice may also be receiving medical treatment for chronic fatigue, fibromyalgia, autoimmune illnesses and or Lyme disease, in addition to bioidentical hormone

replacement therapy.

Family history of cardiac incidence before the age of 55 was identified in fathers more frequently than in other family members, and mothers were the second most commonly found. One patient of the 101 reviewed charts reported cardiac incidence for myocardial infarction prior to Biest and Progesterone compounded prescription use, while one patient experienced sinus tachycardia, one reported history of phlebitis, and one had documented mild mitral regurgitation. There were no reported cardiac incidences for myocardial infarction or stroke post Biest and Progesterone compounded use, however, two patients had reported new onset of atrial fibrillation; two experienced hypertension, and one developed hyperlipidemia.

The initial Progesterone dose in the 101 charts reviewed was 100 mg in 23 (22.8%) patients and 200 mg in 64 (63.4%) of the women, while 200 mg post Progesterone dosage increased to 71 (72.4%) women and the 100 mg dosage of Progesterone decreased to 15 (15.3%) women. There was one (1%) patient taking 50 mg and one (1%) utilizing 400 mg of Progesterone after four years of use. Of the Biest prescription use, 88 (87.1%) women applied a gel based compounded prescription, 12 (11.9%) utilized a cream based compounded prescription, and one (1.0%) used a combination of gel and cream compounded prescription.

Forty patients out of the 101 were screened for bone density while post Biest and Progesterone compounded prescription use there were 43 patients screened for bone density and or C-telopeptide markers, with no change in findings for increase in osteoporosis from initial visit to last visit. The lack of mammography and bone density results may be due to the fact that most of these patients had mammograms or bone density outside of this practice and test results were not regularly forwarded to the medical facility.

Total cholesterol levels were analyzed in 58 of the 101 women after at least four years of

use with Biest and Progesterone compounded prescription. Initial analysis using a paired sample t-test revealed no significant difference between pre prescription Biest and Progesterone use and post BHRT on total cholesterol levels however, there was a significant correlation seen between pre Biest and Progesterone and post BHRT use on total cholesterol levels. The results revealed a decrease in total cholesterol with a mean difference of 4.07 and the *Pearson coefficient* $r(58) = .481, p < .001$ see Table 11.

A paired samples t-test was conducted on low density lipoprotein levels (LDL), in pre Biest and Progesterone compounded prescription use revealing a Mean of 116.83 and a Standard Deviation of 33.64, while the difference between post Biest and Progesterone compounded prescription use on LDL levels revealed a mean of 113.88, and a standard deviation of 29.73. No significant difference was found in LDL cholesterol. A Pearson correlation was conducted between pre BHRT prescription use and post BHRT treatment on LDL cholesterol levels and there was a significant correlation: $r(58) = .416$, and $p = .001$ refer to Table 13.

Summary

This project has expanded research of bioidentical hormone replacement therapy with Biest and Progesterone compounded prescription used for four years or more, with outcomes related to patient safety by evaluating a population of women for breast cancer incidence, cardiac incidence and assessment for bone loss. The focus was to evaluate the use of Biest and Progesterone after a period of time for safety and to identify the effects specific to bone loss, cholesterol levels, cardiac incidence and breast cancer incidence. The results yielded valuable information regarding the impact of Biest and Progesterone on total cholesterol levels, triglycerides, LDL, and HDL levels. There were a few women on lipid-lowering medications on initial visit and this may have a slight impact on the cholesterol results for this study.

The use of Biest and Progesterone compounded prescription treatment for four years or more revealed no breast cancer incidence with the women in the study, however only 25% had mammography reports available while the remaining had self-reported results for negative incidence. Cardiac incidence revealed no reported MI occurred within this population, and cholesterol profiles remained relatively unchanged from the start of treatment to after four years with the exception of a slight decrease in HDL levels. Future studies should include randomized controlled trials that would continue to evaluate women for breast cancer incidence while utilizing Biest and Progesterone therapy. Mammography results would be prudent to have available in future studies. Lastly, future studies should include the use of testosterone replacement therapy concurrently with Biest and Progesterone compounded prescription use in menopausal women.

Limitations

There were a number of limitations identified in this study. One limitation included the tool that had not been previously piloted therefore the validity and reliability of the tool had not been tested. Future projects should include a past medical history, specifically for breast cancer, smoking history, exercise and diet. There was also a lack of identification of the population specific to ethnicity within the patient information no question existed within the initial office visit patient questionnaire. The blood pressures obtained from the women in the study did not include sufficient information to make any conclusions regarding the incidence for hypertension with the prescribed BHRT treatment. Only one blood pressure was obtained from the initial visit and subsequently one from the last visit and three consecutive blood pressures are required to diagnose hypertension according to the JNC 8 guidelines for hypertension (James, et al., 2014).

The practice required payment at the time services were rendered and was an out-of-

network practice. Patients are unable to apply insurance coverage at the time of their visits, resulting in a financial limitation for some patients. The changes in health care has led to concierge medicine which began in 1996, when Dr. Howard Maron, a Seattle Supersonics basketball team doctor, and Dr. Scott Hall decided to offer the same opportunity for luxury care to a selected group of patients (DiGiacomo, 2006). This type of medical care is also referred to as retainer, boutique, luxury primary care, or luxury medicine (Jones & Treiber, 2010). Therefore, the patient population could be considered to be of middle to upper class however no financial information was available about the population. Additionally, this was a retrospective chart review and this was information from one office and not a randomized control study which is the gold standard in research design because it contains the highest level of validity (West, et al., 2008). Another limitation is the lack of available treatment with bioidentical hormone replacement therapy in mainstream medicine because of the controversies and lack of evidence-based support from the Endocrine Society and the American College of Obstetricians and Gynecologists for the use of this treatment for the relief of menopausal symptoms.

Bias

The one bias was patients were selected from an in-office Compounding Four System, excluding patients who obtained their prescriptions from other compounding pharmacies.

Implications for Nursing Practice

There is a lack of evidence-based studies in the medical and advanced practice nursing literature that support the treatment of patients with peri-menopause and menopause symptoms with the use of bioidentical compounded Biest and Progesterone therapy. Throughout the course of researching the literature for this project, there were limited studies which evaluated any bioidentical hormone usage for over a year of continuous use. Since the publication of the

Women's Health Initiative (2002), results women are seeking alternative treatment with bioidentical hormones and the safety of these hormones has not been established according to the literature (Cirigliano, 2007; Ruiz et al., 2011).

References

- American College of Obstetricians and Gynecologists (2012). Committee Opinion No: 532: Compounded bioidentical menopausal hormone therapy. *Obstetrics Gynecology*, 120, 411-415.
- Archer, D. F., Baber, R. J., Barlow, D., Birkhauser, M. H., Brincat, M., Cardozo, L., de Villiers, T. J.,.....Stevenson, J. C. (2011). Updated IMS recommendations on postmenopausal hormone therapy and preventive strategies for midlife health. *Climacteric*, 14, 302-320.
- Banks, E., Beral, V., & Reeves, G. (1999). The million women study: Design and characteristics of the study population. *Breast Cancer Research*, 1(1), 73-80.
- Bastian, L., Smith, C., & Nanda, K. (2003). Is this woman perimenopausal? *JAMA*, 289(7), 890-902.
- Beral, V. (2003). Breast cancer and hormone replacement therapy in the Million Women Study. *Lancet*, 362(9382), 419-427.
- Bergkvist, L., Adami, H. O., Persson, I., Bergstrom, R., & Krusemo, U. B. (1989). Prognosis after breast cancer diagnosis in women exposed to estrogen and estrogen-progesterone replacement therapy. *American Journal of Epidemiology*, 130(2), 221-228.
- Boothby, L. A., Doering, P. L., & Kipersztak, S. (2004). Bioidentical hormone therapy: A review. *Menopause*, 11, 356-367.
- Bosarge, P. & Freeman, S. (2009). Bioidentical hormones, compounding, and evidence-based medicine: What women's health practitioners need to know. *Journal of Nurse Practitioners*, 5(6), 421-427.
- Brockie, J. (2008). Physiology and effects of the menopause. *Nurse Prescribing*, 6(5), 202-207.
- Buist, D. M., Newton, K. M., Miglioretti, D. L., Beverly, K., Connelly, M. T., & Andrade, S.

- (2004). Hormone therapy prescribing patterns in the United States. *Obstetrics & Gynecology*, 104, 1042-1050.
- Bushnell, C. (2009). Hormone therapy and stroke: Is it all about timing? *Current Treatment Options Cardiovascular Medicine*, 11(3), 241–250.
- Canonico, M., Oger, E., Plu-Bureau, G. (2007). Hormone therapy and venous thromboembolism among postmenopausal women: Impact of the route of estrogen administration and progestogens: The ESTHER study. *Circulation*, 115, 840-845.
- Chlebowski, R. T. & Anderson, G. L. (2012). Changing concepts: Menopausal hormone therapy and breast cancer. *Journal National Cancer Institute*, 104, 517-527.
- Christenson, E. S., Jiang, X., Kangan, R., & Schnatz, P. (2012). Osteoporosis management in post-menopausal women. *Minerva Ginecol*, 64(3), 181-194.
- Cirigliano, M. (2007). Bioidentical hormone therapy a review of the evidence. *Journal of Women's Health*, 16(5), 600-631.
- Colditz, G. A., Hankinson, S. E., Hunter, D. J., Willett, W. C., Manson, J. E., Stampfer, M. R., .. Spetzer, F. E. (1995). The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *New England Journal of Medicine*, 332(24), 1589-93.
- Curb, J. D., Prentice, R. L., Bray, P. F., Langer, R. D., Van Horn, L., Barnabei, V. M.,..... Rosendaal, F. R. (2006). Venous thrombosis and conjugated equine estrogens in women without a uterus. *Archives Internal Medicine*, 166(7), 772-780.
- Cushman, M., Kuller, L. H., & Prentice, R. (2004). Estrogen plus progestin and risk of venous thrombosis. *JAMA*, 292, 1573-1580.
- DeFronzo, R. A. (1997). Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerosis. *Neth Journal Med*, 50, 191-197.

de Lecinana, M., Egido, J., & Fernandez, C. (2007). Risk of ischemic stroke and lifetime estrogen exposure. *Neurology*, 68, 33-38.

Department of Health and Human Services (DHHS). (2004). *Bone Health and Osteoporosis: A Report of the Surgeon General*. Rockville, MD: U. S. Department of Health and Human Services. Office of the Surgeon General.

Despres, J. P., Moorjani, S., Lupien, P. J., Tremblay, A., Nadeau, A., & Bouchard, C. (1990). Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. *Arteriosclerosis*, 10, 497-511.

Despres, J. P. (1993). Abdominal obesity as important component of insulin-resistance syndrome. *Nutrition*, 9, 452-459.

DiGiacomo, M. (2006). Concierge practices: Paying the price for premium healthcare. *Physical Therapy*, 14(7), 68-70.

Eichelsdoerfer, P. E. (2008). Prescribing compounded bioidentical hormones: Antiaging applications. *Integrative Medicine*, 7(3), 43-48.

Endocrine Society. (2006). Bioidentical Hormones Position Statement. Retrieved from: <https://www.endocrine.org/~media/endosociety/Files/Advocacy%20>

Files, J. A., Ko, M. G., & Pruthi, S. (2011). Bioidentical hormone therapy. *Mayo Clinic Proceedings*, 86(7), 673-680.

Food and Drug Administration (FDA) (2012). Update on fungal meningitis: FDA provides NECC customer list. Retrieved from: <http://www.fda.gov/Drugs/DrugSafety/ucm>

Franco, M., Cooper, R. S., Bilal, U., & Fuster, V. (2011). Challenges and opportunities for cardiovascular disease prevention. *The American Journal of Medicine*, 124(2), 95-102.

Franklin, R. M., Ploutz-Snyder, L., & Kanaley, J. A. (2009). Longitudinal changes in abdominal fat distribution with menopause. *Metabolism Clinical and Experimental*, 58, 311-315.

- Fugh-Berman, A. & Bythrow, J. (2007). Bioidentical hormones for menopausal hormone therapy: Variation on a theme. *Society of General Internal Medicine*, 22, 1030-1034.
- Garnero, P., Sornay-Rendu, E., Duboeuf, F., & Delmas, P. D. (1999). Markers of bone turnover Predict postmenopausal forearm bone loss over four years: The OFELY Study. *Journal Bone Mineral Research*, 14(9), 1614-1621.
- Ganero, P. (2008). Biomarkers for osteoporosis management: Utility in diagnosis, fracture risk prediction and therapy monitoring. *Molecular Diagnostic Therapy*, 12(3), 157-170.
- Garard, R., Burger, H., & Davison, S. (2011). Exploring the hormone replacement therapy debate. *Australian Nursing Journal*, 19(5), 30-33.
- Garber, A. (2008). Compounded hormones therapies: Unproven, untested – and unpopular. *Endocrine Today*, 6(5), 12-14.
- Hall, L., Callister, L. C., & Berry, J. A. & Matsumura, G. (2007). Meanings of menopause: Cultural influences on perception and management of menopause. *Journal of Holistic Nursing*, 25(2), 106-118.
- Herrington, D. M., Reboussin, D.M., Brosnihan, K. B., Sharp, P. C. Shumaker, S. A., Snyder, T.Waters, D. (2000). Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *The New England Journal of Medicine*, 343(8), 522-529.
- Hickey, M., Davis, S. R., & Sturdee, D. W. (2005). Treatment of menopausal symptoms: What shall we do now? *Lancet*, 366, 409-21.
- Holloway, D. (2011). An overview of the menopause: Assessment and management. *Nursing Standard*, 25(30), 45-58.
- Hoover, R., Gray, L. A., Cole, P., & MacMahon, B. (1976). Menopausal estrogens and breast cancer. *Advance. Exp Med Bio*, 36(0), 113-136.

- Hu, F., Grodstein, F., & Nennekens, C. (1999). Age at natural menopause and risk of cardiovascular disease. *Archives Internal Medicine*, 159, 1060-1066.
- Im, E. O. (2013). Transition theory. In R. R. Alligood, & A. M. Tomey (Eds.), *Nursing Theorists and Their Work* (8th ed.). (372-395). St Louis, MO: Mosby.
- Im, E. O. & Meleis, A. I. (2000). Meanings of menopause: Low-income Korean immigrant women. *Western Journal of Nursing Research*, 22(1), 84-102.
- International Menopause Society Writing Group (IMSWG). (2011). Updated IMS recommendations on postmenopausal hormone therapy and preventive strategies for midlife health. *Climacteric*, 14, 302-320.
- Islam, S., Liu, Q., Chines, A., & Hetzer, E. (2009). Trend in incidence of osteoporosis-related fractures among 40-69-year-old women: Analysis of a large insurance claim database. *Menopause*, 16, 77-83.
- Jackson, G. (2008). Gender differences in cardiovascular disease prevention. *Menopause International*, 14, 13-17.
- Jacobsen, B., Heuch, I., & Kvale, G. (2004). Age at natural menopause and stroke mortality: Cohort study with 3561 stroke deaths during 37-year follow-up. *Stroke*, 35, 1548-1551.
- James, P. A., Oparil, S., Carter, B., Cushman, W., Dennison-Himmelfarb, C. , Handler, J.,.....Ortiz, E. (2014). 2014 Evidence-based guideline for the management of high blood pressure in adults report from the panel members appointed to the eighth joint national committee (JNC 8). *JAMA*, 311(5), 507-520.
- Jones, J. H., & Treiber, L. (2010). Concierge medicine: The perfect storm? Implications for Nurse Practitioners. *The Journal for Nurse Practitioners*, 6(2), 109-114.
- Kanaya, A. M., Herrington, D., Vittinghoff, E., Lin, F., Grady, D., Bittner, V.,

- Barrett-Connor, E. (2003). Glycemic effects of postmenopausal hormone therapy: The heart and estrogen progestin replacement study. A randomized, double-blind, placebo-controlled trial. *Annals Internal Medicine*, 138, 1-9.
- Karim, R., Dell, R. M., Greene, D. F., Mack, W. J., Gallagher, J. C., & Hodis, H. N. (2011). Hip fracture in postmenopausal women after cessation of hormone therapy: Results from a prospective study in a large health management organization. *Menopause*, 18, 1172-1177.
- LaCroix, A. Z., Chlebowski, R. T., & Manson, J. E. (2011). Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: A randomized controlled trial. *JAMA*, 305, 1305-1314.
- Lewis, V. (2009). Undertreatment of menopausal symptoms and novel options for comprehensive management. *Current Medical Research Opinion*, 25(11), 2689-2698.
- Lindsay, R. (2004). Hormones and bone health in postmenopausal women. *Endocrine*, 24(3), 223-230.
- Lobo, R. A. (2013). Where are we 10 years after the Women's Health Initiative? *Journal Clinical Endocrinology Metabolism*, 98(5), 1771-1780.
- Lorentzen, J. (2001). Hormone replacement therapy: Part 1 the evolution of hormone treatment. *International Journal of Pharmaceutical Compounding*, 5(5), 336-338.
- Louet, J., LeMay, C., & Mauvais-Jarvis, F. (2004). Antidiabetic actions of estrogen: Insight from human and genetic mouse models. *Current Atherosclerosis Reports*, 6, 180-185.
- Mahmud, K. (2010). Natural hormone therapy for menopause. *Gynecological Endocrinology*, 26(2), 81-85.

Manson, J. E., Hsia, J., Johnson, K. C., Rossouw, J. E., Assaf, A. R., Lasser, N. L.,.....

Cushman, M. The Women's Health Initiative Investigators. (2003). Estrogen plus progestin and the risk of coronary heart disease. *New England Journal of Medicine*, 349, 523-534.

Margolis, K. L., Bonds, D. E., Rodabough, R. J., Tinker, L., Phillips, L. S., Allen, C.,...Howard, B. V. (2004). Effect of estrogen plus progestin on the incidence of diabetes in postmenopausal women: Results from the women's health initiative hormone trial. *Diabetologica* 47, 1175-1187

Marnocha, S. K., & Berstrom, M., & Dempsey, L. F. (2011). The lived experience of perimenopause and menopause. *Contemporary Nurse*, 37(2), 229-240.

Melby, M. K., Lock, M., & Kaufert, P. (2005). Culture and symptom reporting at menopause. *Human Reproductive Update*, 11, 495-512.

Meleis, A. I., Sawyer, L. M., Im, E. O., Messias, D. K., & Schumacher, K. (2000). Experiencing transitions: An emerging middle-range theory. *Advance Nursing Science*, 23(1), 12-28.

Meleis, A. (2006). Transition theory. In M. R. Alligood & A. M. Tomey (Eds.), In Nursing, theorists and their work (pp. 416-433). Retrieved from:
<https://www.us.elsevierhealth.com/.../us/samplechapters/.../Chapter%2020>.

Meleis, A. I. (2010). Developmental transitions In Meleis, *Transitions theory: middle-range and situation-specific theories in nursing research and practice* (121-129). Retrieved from:
taskurun.files.wordpress.com/.../transitions_theory__middle_range_and

Miller, M. M. & Franklin, K. B. (1999). Theoretical basis for the benefit of postmenopausal estrogen substitution. *Experimental Gerontology*, 34(5), 587-604.

Morrow, P. K. H., Mattair, D. N., & Hortobagyi, G. N. (2011). Hot flashes: A review of

- pathophysiology and treatment modalities. *The Oncologist*, 16, 1658-1664.
- Nakano, K., Pinnow, E., Flaws, J. A., Sorkin, J. D., & Gallicchio, L. (2012). Reproductive history and hot flashes in perimenopausal women. *Journal of Women's Health*, 21(4), 433-439.
- National Institutes of Health. (2005). National Institutes of Health State-of-the Science Conference Statement: Management of menopause-related symptoms. *Archives of Internal Medicine*, 142, 1003-1013.
- National Osteoporosis Foundation. (2008). *Clinician's Guide to Prevention and Treatment of Osteoporosis*. Washington, DC: National Osteoporosis Foundation. Retrieved from: http://www.nof.org/professionals/NOF_Clinicians_Guide.pdf.
- Nelson, H. D. (2008). Menopause. *Lancet*, 371 (March 1), 760-770.
- Norris, L. A., Joyce, M., O'Keefe, N., Sheppard, B. L., & Booner, J. (2002). Haemostatic risk factors in healthy postmenopausal women taking hormone replacement therapy. *Maturitas*, 43, 125-133.
- North American Menopause Society (NAMS). (2005). Menopause health questionnaire. Retrieved from: www.menopause.org/docs/default-document-library/questionnaire.pdf
- North American Menopause Society (NAMS). (2007). *Menopause Practice: A Clinician's Guide* (3rd ed.). Cleveland, OH: North American Menopause Society.
- North American Menopause Society (NAMS). (2010). Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause: The Journal of The North American Menopause Society*, 17(1), 25-54.
- North American Menopause Society (NAMS). (2013). Position Statement: Management of

- symptomatic vulvovaginal atrophy. *Menopause*, 20(9), 888-902.
- Olie, V., Plu-Bureau, G., Conrad, J., Horellou, M. H., Canonico, M., & Scarabin, P. Y. (2011). Hormone therapy and recurrence of venous thromboembolism among postmenopausal women. *Menopause*, 18, 488-493.
- Parke, A. & Abernethy, K. (2008). Hormone replacement therapy: Risks and benefits. *Nurse Prescribing*, 6(10), 433-439.
- Pegues, D. A. (2006). Improving and enforcing compounding practices to protect patients. *Clinical Infectious Disease*, 43, 838-840.
- Pike, M. C., Kralio, M. D., Henderson, B. E., Casagrande, J. T., & Hoel, D. G. (1983). Hormonal risk factors, breast tissue age and the age-incidence of breast cancer. *Nature*, 303(5920), 767-770.
- Plonczynski, D. J. & Plonczynski, K. J. (2007). Hormone therapy in perimenopausal and postmenopausal women. *Journal of Gerontological Nursing*, 33(5), 48-55.
- Radiological Society of North America (RSNA). (2014). Bone densitometry.1-6. Retrieved from:www.radiologyinfo.org
- Rees, M., Stevenson, J., Hope, S., Rozenburg, S., & Palacio, S. (2009). *Management of the Menopause* (5th ed.). British Menopause Society of Medicine, London.
- Rosenthal, M. S. (2008). Ethical problems with bioidentical hormone therapy. *International Journal of Impotence Research*, 20, 45-52.
- Ross, R. K., Paganini-Hill, A., Gerkins, V. R., Mack, T. M., Piffeffer, R., Arthur, M., & Henderson, B. E. (1980). A case-control study of menopausal estrogen therapy and breast cancer. *The Journal of the American Medical Association*, 243(16), 1635-1639
- Rossouw, J. E., Anderson, G. L., Prentice, R. L., LaCroix, A. Z., Kooperberg, C., Stefanick, M.

- L....Ockene, J. Writing Group for the Women's Health Initiative Investigators. (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *JAMA*, 288, 321-333.
- Rossouw, J. E., Prentice, R. L., Manson, J. E., Wu., Barad, D., Barnabei, D.,...Stefanick, M. L. (2007). Postmenopausal hormone therapy and the risk of cardiovascular disease by age and years since menopause. *JAMA*, 208, 465-1477.
- Ruiz, A. D., Daniels, K. R., Barner, J. C., Carson, J. J., & Frei, C. R. (2011). Effectiveness of compounded bioidentical hormone replacement therapy: An observational cohort study. *BioMed Central Women's Health*, 11(27), 1-10.
- Sare, G. M., Gray, L. J., & Bath, P. M. (2009). Association between hormone replacement therapy and subsequent arterial and venous vascular events: A meta-analysis. *European Heart Journal*, 29, 2031-2041.
- Savage, P. (2012). Ensuring the safety of compounded products: Best clinician practices and an existing solution. *Integrative Medicine*, 11(6), 17-20.
- Schenck-Gustafsson, K. (2007). Diagnosis of cardiovascular disease in women. *Menopause International*, 13(1), 19-22.
- Schierbeck, L.L., Rejnmark, L., Tofteng, C. L., Stilgren, L., Eiken, P., Mosekilde, L.,. Jensen, L. E. (2012). Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: Randomized trial. *BMJ*, 345:e6409.
- Shoupe, D. (2012). Individualizing hormone therapy: Weighing risks and benefits. *Contemporary OB/GYN*, August 1, 16-24. Retrieved from:
contemporaryobgyn.modernmedicine.com

- Sites, C. K. (2008). Bioidentical hormones for menopausal therapy. *Women's Health*, 4(2), 163-171.
- Smith, A. L. & Wein, A. J. (2010). Estrogen replacement therapy for the treatment of post-menopausal genitourinary tract dysfunction. *Discovery Medicine*, 10(55), 500-510.
- Sood, R., Warndahl, R. A., Schroeder, D. R., Singh, R. J., Rhodes, D. J., Wahner-Roedler, D., . & Shuster, L. T. (2013). Bioidentical compounded hormones: A pharmacokinetic evaluation in a randomized clinical trial. *Maturitas*, 74, 375-382.
- Sprague, B. L., Trentham-Dietz, A., & Cronin, K. A. (2012). A sustained decline in post-menopausal hormone use: Results from the National Health and Nutrition Examination survey. *Obstet Gynecol*, 120, 595-603.
- Stevenson, J. C., Hodis, H. N., Pickar, J. H., & Lobo, R. A. (2009). Coronary heart disease and menopause management: The swinging pendulum of HRT. *Atherosclerosis*, 207, 336-340.
- Stuenkel, C. A., Gass, M. L., Manson, J. E., Lobo, R. A., Pal, L., Rebar, R. W., & Hall, J. E. (2012). A decade after the Women' health initiative-the experts do agree. *Fertility and Sterility*, 98(2), 313-314.
- The Writing Group for the PEPI Trial. (1996). Effects of hormone therapy on bone mineral density: Results from the postmenopausal estrogen/progestin interventions (PEPI) trial. *JAMA*, 276(17), 1389-1396.
- Toth, M. J., Tchernof, A., Sites, C. K. & Poehlman, E. T. (2000). Menopause-related changes in body fat distribution. *Annals of the New York Academy of Sciences*, 904, 502-506.
- U. S. Census Bureau. (2010). *Profile of general population and housing characteristics: 2010 demographics profile data*. Retrieved from:

<http://factfinder2.census.gov/faces/tableservices/jst/pages/productview.xhtml?pid>

U. S. Food and Drug Administration (USFDA). (2008). FDA takes action against compounded menopause hormone therapy drugs. Silver Spring (MD) Retrieved from:

<http://www.fda.gov/News>

U. S. Preventive Services Task Force. (2012). Menopausal hormone therapy for the primary prevention of chronic conditions: Recommendation Statement. *Annals Internal Medicine*, 158(1), 47-54.

Walker, C. R. (2001). Bioidentical hormone replacement therapy. A natural option for perimenopause and beyond. *Advance Nurse Pract.* 9(5), 39-42, 45.

Walsh-Childers, K., Edwards, H., & Grobmyer, S. (2011). Covering women's greatest health fear: Breast cancer information in consumer magazines. *Health Community*, 26, 209-220.

Warren, M. P. & Valente, J. S. (2004). Menopause and patient management. *Clinical Obstet Gynecology*, 47, 450-740.

Watt, P. J., Hughes, R. B., Rettew, L. B., & Adams, R. (2003). A holistic programmatic approach to natural hormone replacement. *Family & Community Health*, 26(1), 55-63.

Weinberg, N., Young, A., Hunter, C. J., Agrawal, N., Mao, S. & Budoffet, M. J. (2012). Physical activity, hormone replacement therapy, and the presence of coronary calcium in midlife women. *Women's Health*, 52, 423-436.

West, S. J., Duan, N., Pequegnat, W., Gaist, P., Des Jarlais, D. C., Holtgrave, D.,.....Mullen, P. (2008). Alternatives to the randomized controlled trial. *American Journal of Public Health*, 98(8), 1359-1366.

Wright, J. & Morganthaler, J. (1997). *Natural Hormone Replacement for Women Over 45*. Petaluma, California: Smart Publications.

Wright, J. (2005). Bio-identical steroid hormone replacement: Selected observations from 23 years of clinical and laboratory practice. *Annals of the New York Academy of Science*, 1057, 506-524.

Wright, J. V. & Leonard, L. (2010). *Stay Young & Sexy with Bio-identical Hormone Replacement*. (2nd ed.). Petaluma, California: Smart Publications.

Wyeth. (2014). History of Wyeth. Retrieved from: www.wyeth.co.za/Home/AboutWyeth/

Yap, D. (2014). How new compounding, track-and-trace law may affect pharmacists: FDA issues pharmacy compounding draft guidance. *Pharmacy Today*, January 1, 2014.

Appendix A

CHART REVIEW TOOL					Page 1
Assessment Information		Assessment Findings			
De-identified Number Assigned					
1	Initial Visit Age	Age Initial visit		Age Last visit	
2	Marital Status	Single	Married	Divorced	
		Separated	Widowed		
3	Symptoms @ Initial Visit				
4	Weight @ initial & last visit	Initial	Last		
5	Menopause induced surgeries	No	Yes		
		Total hysterectomy Date:			
		Partial hysterectomy Date:			
6	Current Medications being used	1. 2. 3. 4. 5. 6. 7.			
6a	Medications used on during last visit	1. 2. 3. 4. 5. 6. 7.			
7	Date initiating BHRT (prescribed)	Month	Year		
8	BHRT dosage of Progesterone & if cycles	Dosage	Yes Cycles		
		No Cycling	Days of cycling		
8a	BHRT dosage of Progesterone & if cycles	Dosage	Yes Cycles		
		No Cycling	Days of cycling		
9	BHRT route of Progesterone prescribed	Oral	Gel	Cream	

10	BHRT dosage of Biest	Initial		Change			
10a	BHRT route of Biest prescribed	Topical Gel Vaginal Sublingual	Cream Oral Drops				
11	BHRT dosage of Biest (current)						
11a	BHRT route of Biest prescribed	Topical Gel Vaginal Sublingual	Cream Oral Drops				
12	Bone density or CTX documented	Yes	No	Results:			
13	Bone density or CTX documented post BHRT	Yes		Results:			
		No					
14	Mammography results prior to BHRT documented	Yes		No			
15	Mammography results/documented post BHRT what year	Yes	No	Year			
		Results negative		Results positive			
17	B/P initial Visit	B/P					
17a	B/P last Visit	B/P					
18	Family history for cardiac disease Mother, father, brother, sister before 55 years of age	Yes	No	Condition:			
		Family member: Mother_____ Father_____ Brother_____ Sister_____					
19	Cardiac incidence prior to BHRT	No	Yes	Condition:			
19a	Cardiac incidence since BHRT	No	Yes	Condition:			
20	Cholesterol screening Initial	Yes	No	Total Chol	HDL	LDL	TRI
		Date Results					
20a	Cholesterol screening following BHRT Date Results_____	Yes	No	Total Chol	HDL	LDL	TRI

Appendix B



CENTERS FOR HORMONE IMBALANCE, HYPOTHYROIDISM AND FATIGUE

September 24, 2014

To: California State University, Fresno Committee of the Protection of Human Subjects

Re: Maria D. White's Doctor of Nursing Practice Project

I, Kent Holtorf M.D., medical director and owner of the Holtorf Medical Group am writing this letter as verification of full support for Maria White's BHRT retrospective study. I am therefore confirming by this written letter no Institutional Review Board (IRB) approval within this office setting is required. The office is located at 23456 Hawthorne Blvd Torrance, CA and I can be reached at 310-375-2705, if you have any further questions.

Respectfully,

A handwritten signature in black ink, appearing to be "KH", written over a horizontal line.

Kent Holtorf, M. D.

Appendix C

California State University,
Fresno School of Nursing
IRB Approval

Date: November 14, 2014

RE: DNP1423 – Bio identical Hormones Utilized for Treating Menopausal Symptoms: Are They Safe?

Dear Maria White,

As the Chair of the Department of Nursing Research Committee, serving as the Institutional Review Board for the Department of Nursing, I have reviewed and approved your review request for the above-referenced project for a period of 12 months. I have determined your study to meet the criteria for EXEMPT IRB review.

Under the Policy and Procedures for Research with Human Subjects at California State University, Fresno, your proposal meets exempt criteria according to section

3.5.2.C: Research involving the collection or study of existing data, documents, records, pathological specimens or diagnostic specimens, if these sources are routinely available to the investigator, and are recorded by the investigator in such a manner that makes identification of the subjects impossible.

The Research Committee may periodically wish to assess the adequacy of research process. If, in the course of the study, you consider making any changes in the protocol or consent form, you must forward this information to the Research Committee prior to implementation unless the change is necessary to eliminate an apparent immediate hazard to the research participant(s).

This study expires: November 14, 2015

The Research Committee is authorized to periodically assess the adequacy of the consent and research process. All problems having to do with subject safety must be reported to the Research Committee. Please maintain proper data control and confidentiality.

If you have any questions, please contact me through the CSU, Fresno School of Nursing Research Committee at tereag@csufresno.edu.

Sincerely,

Terea Giannetta, DNP
Department of Nursing, Research Committee, Chair